REMARKS

Upon entry of this amendment claims 2-3, 6-15, 18-26, 29-32 and 64-76 are pending. Claims 1 and 63 been cancelled and are no longer pending. Claims 4-5, 16-17, 27-28 and 33-62 were previously canceled. Claim 22 has been amended. Support for the amendment of claim 22 may be found in the specification.[1]

Claims 33-49 and claims 50-62 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/11/2007. New claims 64-76 correspond to original claims 33-34, 37-42 and 45-49 but have been amended to ultimately depend from claim 22. Support for claims 64-76 may be found in the specification.[2] Thus, pursuant to M.P.E.P. §821.04, applicants request rejoinder of withdrawn claims 64-76 as they depend from claim 22 and therefore require all the limitations of claim 22.

Regarding the Examiner's comments relating to product-by-process claims, claim 20 has been amended to delete product-by-process limitations.

The Invention

The invention encompasses a pharmaceutical composition comprising sodium 4-phenylbutyrate, at least one water soluble sweetening agent comprising a mixture of aspartame and potassium acesulfame, and at least one water soluble flavoring agent, the amounts being selected so as to mask substantially the bitter taste and pungent odor of sodium 4-phenylbutyrate.[3] The invention may also be a dry powder pharmaceutical composition,[4] which may or may not comprise granules comprising sodium 4-phenylbutyrate.[5] Furthermore the invention may also be a concentrated aqueous solution.[6]

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[1] Specification as filed, page 4, lines 24-40, page 5, lines 5-16, page 5 lines 29-40, page 8, lines 8-31 and original claims 20-21, 33, 40 and 47
[2] Specification as filed, page 5 lines 29-40, page 8, lines 8-31 and original claim 33
[3] Claim 10
[4] Claims 2, 3, 6 and 7
[5] Claim 11
[6] Claim 13

The invention further encompasses a unit dose for administration to a patient requiring treatment for a urea cycle deficiency according to a regime in which the patient is administered a predetermined number of doses daily corresponding to from about 450 to about 600 mg/kg/day of sodium 4-phenylbutyrate.[7] The invention also encompasses a pharmaceutically acceptable aqueous solution ready for administration to such a patient.[8] The invention further encompasses a method of treating a patient suffering from a condition selected from a urea cycle deficiency and sickle-cell anemia which comprises administering to the patient in one or more unit doses daily a pharmaceutical composition.[9]

The invention provides an improved pharmaceutical composition containing sodium 4-phenylbutyrate for use in the treatment of patients suffering from urea cycle deficiencies and sickle-cell anemia. Specifically, there is a need for an improved method of oral administration for the treatment of sickle-cell anemia and in particular for the treatment of urea cycle deficiencies as well as of sickle-cell anemia.

The passages at pages 1 to 3 of the description discuss the problems associated with treating these diseases as well as sickle cell anemia with sodium 4-phenylbutyrate. As indicated, sodium 4-phenylbutyrate is a very bitter compound and has the pungent odor of mice. Whilst adults would find this difficult to take, it is completely unacceptable to children who have to take large amounts of the medicine every day. As set out in the description, a 6 year old child weighing 19 kg typically has to take 3.8 g of powder 3 times daily. If the child fails to take one of the doses they then become nauseous meaning that they cannot take their medicine and an intravenous infusion is required. This requires admission to a hospital. Delay in reaching the hospital can lead to hyperammonaemic coma which can lead to death or brain damage. Thus, the present invention provides a preparation capable of delivering the requisite dose of sodium 4-phenylbutyrate in a form readily acceptable to young patients and

[7] Claim 20
[8] Claim 22
[9] Claim 64

measurable with suitable accuracy which ultimately improves patient compliance and minimizes the need for frequent hospitalization.

It is important that small children cannot take tablets. Medication therefore needs to be given in a formulation in liquid form. Generally this is provided as a powder which is then made up into a liquid by a pharmacist and then usually further diluted by the caretaker of the child. Thus, the problem addressed by the present invention is to provide the sodium 4-phenylbutyrate in a formulation which a chronically ill child will take, which is a significant problem when large doses of a bitter, salty medicine in liquid form which smells like a rodent must be consumed each day from birth. The invention is not one which merely identifies a sweetener that will resolve the problem of a bitter, nasty or disagreeable tasting medicine. Even more importantly, the invention provides a formulation which provides the required level of medication, is palatable to small children and which does not cause other health problems by increasing, for example, the salt intake to the child. Therefore, applicants are not simply trying to patent the concept of "a spoonful of sugar making the medicine go down."

I. 35 U.S.C. 103(a) Rejections

Reconsideration is requested of the rejection of claims 1-3, 6, 10, and 63 under 35 U.S.C. 103(a) as being unpatentable over Samid et al. (US Patent No. 6,037,376), in view of Rubenstein et al. (US 2002/0115619), and further in view of D'Silva (US 6,550,955). Claims 1-3, 6, 10, and 63 essentially encompass a pharmaceutical composition comprising sodium 4-phenylbutyrate, at least one aromatic flavoring agent, and at least one synthetic sweetening agent comprising a mixture of aspartame and potassium acesulfame being selected so as to mask substantially the bitter taste and pungent odor of sodium 4-phenylbutyrate.

Samid is relied upon as disclosing pharmaceutical compositions comprising sodium phenylbutyrate, a water soluble sweetener, sugar and a binder, but is said not to teach an aromatic flavoring agent or the combination of

aspartame and potassium acesulfame.[10] Rubenstein is relied upon as teaching that sodium 4-phenylbutyrate causes a bad taste in the mouth, and can be formulated as a tablet containing a sweetener, a flavorant or "some combinations thereof in order to provide a pharmaceutically elegant and palatable preparation." D'Silva is relied upon for teaching that flavors and sweeteners are added to medicinal compounds with unpleasant taste, and that such sweeteners include aspartame, acesulfame, saccharin, sucralose or mixtures, and fruit flavorants. It is said that it would have been obvious for a person skilled in the art at the time of the invention to employ aromatic flavoring agents and specific synthetic sweetening agents in compositions comprising sodium 4-phenylbutyrate taught by Samid et al because Rubenstein taught that sodium 4-phenylbutyrate has a bad taste and that flavorings and sweeteners can be used and that D'Silva teaches that aspartame, acesulfame, potassiumsaccharine, sucralose and fruit flavors can be used to mask disagreeable taste of the pharmaceutically active agent.[11]

Samid discloses in Examples 18 and 21, pharmaceutical compositions which comprise sodium 4-phenylbutyrate. Example 18 relates to a tablet formulation. In general, since tablets can be taken quickly by an adult, the taste and odor issues are not as problematic as they are in formulating something that will be taken as a liquid by a child. Thus the formulation of Example 18, whilst indicating that sodium 4-phenylbutyrate may be used in a pharmaceutical does not give any suggestion that it can be provided to a small child in liquid form. Furthermore, Samid does not suggest that there is a problem associated with the taste and smell of sodium 4-phenylbutyrate nor does it suggest how these problems should be addressed. Likewise, Example 21 of Samid relates to a lotion and does not address the taste and odor problems. As acknowledged by the Examiner, Samid does not disclose an aromatic flavoring or suggest the particular mixture of synthetic sweetening agents aspartame and potassium

[10] See page 3 of Office action.
[11] Examiner's comments on page 4 in the Office Action.

acesulfame to mask the bitter, salty, nasty or disagreeable taste or the pungent rodent-like odor of sodium 4-phenylbutyrate.[12]

Although Rubenstein discloses that sodium 4-phenylbutyrate causes a bad taste in the mouth, he does not teach or suggest that the particular combination of sweeteners and flavorant as claimed will mask the pungent rodent-like odor of sodium 4-phenylbutyrate. As noted above, the rodent-like odor of this particular drug needs to be masked in a powder, granular or liquid pharmaceutical composition for administration to patients including children. Rubenstein's tablets do not address the odor problem encountered in formulating these compositions.

D'Silva's general teaching of the use of sweeteners and flavorants to mask unpleasant taste of a pharmaceutical also fails to recognize the odor problem associated specifically with sodium 4-phenylbutyrate. What was not known from D'Silva or the other cited references and indeed the industry has struggled with for many years was what could be used to mask the extremely salty taste and the pungent rodent-like smell of an aqueous composition comprising sodium 4-phenylbutyrate that might be made from granules or powder which is to be taken up to four times daily from birth until the children can swallow tablets.

The cited references, when considered alone or in combination, fail to provide one skilled in the art with a reason to formulate a dry powder, granules, solution or concentrate as claimed, let alone with any reasonable expectation of success. The references regarding sodium 4-phenylbutyrate, Samid and Rubenstein, do not suggest dosage forms as claimed, but rather only describe tablets, a dosage form which cannot be taken by children. These references also fail to disclose or suggest that the odor of the drug can be masked by the mixture of sweeteners and a flavorant as claimed. The cited references would not have led one skilled in the art to select the specific combinations of flavoring agent, and at least one synthetic sweetening agent comprising a mixture of aspartame and potassium acesulfame in the amounts to mask the pungent rodent-like odor of sodium 4-phenylbutyrate. Furthermore, the invention comprises the selection

[12] Examiner's comments on page 3 in the Office Action and the remainder of the Office Action.

of the two sweeteners and the flavorant to avoid not only the pungent rodent-like odor but also the disagreeable taste of the sodium associated with high doses of sodium 4-phenylbutyrate.

Nor is there a basis for obviousness under the recently articulated *KSR* guidelines. To reject a claim based on this rationale, Office personnel must articulate the following: (1) a finding that at the time of the invention, there had been a recognized problem or need in the *art* which may include a design need or market pressure to solve a problem; (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem; (3) a finding that one of ordinary skill in the *art* could have pursued the known potential solutions with a reasonable expectation of success: and (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration.[13]

At the time of the invention, there were a multiplicity of sweeteners and flavors to choose from with the goal of possibly masking the disagreeable taste of sodium 4- phenylbutyrate. The sheer number of possible combinations and/or permutations suggests the absence of a finite number of sweeteners to choose from, and there was no predictable solution with regard to odor masking for sodium 4-phenylbutyrate, as evidenced by the Samid and Rubenstein references which fail to mention the odor problem let alone recognize the solution to the problem. Thus, it would have been unreasonable to have any expectation of success particularly with regard to masking the pungent rodent-like odor of sodium 4- phenylbutyrate because none of the references relied on specifically taught or suggested that specific sweeteners and flavors could achieve the stated goal. Therefore, it would not have been obvious to select the flavorants and mixture of aspartame and potassium acesulfame sweeteners in amounts to achieve the dual goal of masking the pungent rodent-like odor and the disagreeable taste of sodium 4- phenylbutyrate.

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[13] Page 7 of The Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR *International Co.* v. *Teleflex,* Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices

The Office asserts that the cited references suggest the claimed pharmaceutical compositions and that the properties of such claimed compositions will also be rendered obvious, since the properties, namely to mask substantially the bitter taste and pungent odor of sodium 4-phenylbutyrate, are inseparable from its composition.[14] Essentially, the Office is characterizing the masking properties of the composition as being inherent in the composition resulting from the combination of the cited references. As noted in M.P.E.P. §2112.IV, a rejection based upon the inherency of a claimed element must be supported by evidence that the missing element is necessarily present in the reference:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). . . .
> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the preform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was biaxially oriented. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented

[14] Examiner's comments on page 4 in the Office Action

> synthetic plastic material." *Id.* at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

Inherency cannot be established by probabilities or possibilities and there is no evidence of record that the masking of odor by the claimed composition would have necessarily and inevitably resulted from the selection of flavoring agents and a mixture of aspartame and potassium acesulfame in a composition comprising sodium 4- phenylbutyrate. Nor is such masking of odor recognized in the art, particularly given that none of the cited references address the odor problem. In light of the above, applicants respectfully submit that claims 1-3, 6, 10, and 63 are not rendered obvious by the combination of Samid, in view of Rubenstein, and further in view of D'Silva.

The Office has not cited any evidence of the use of sweeteners and flavorants in amounts sufficient to mask the pungent rodent-like odor of sodium 4-phenylbutyrate. To the extent that the Office relies upon optimization of the amounts being routine to one of ordinary skill, MPEP 2144.05 makes it clear that the cited reference must recognize the parameter at issue to be a result effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of the variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Thus, only the optimization of "result-effective variables," as recognized in the prior art, might be characterized as routine. MPEP 2144.05 II B. None of the references relied on by the Examiner disclose nor suggest that the masking of the pungent rodent-like odor of sodium 4-phenylbutyrate is a result effective variable and thus it was not obvious to determine or optimize parameters such as amounts of flavoring agents, sweetening agents, and binding agent to affect the pungent rodent-like odor of sodium 4-phenylbutyrate.

Reconsideration is requested of the rejection of claims 1-3, 6-15, 18-26, 29-32, and 63 which are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubenstein in view of D'Silva. Claims 1-3, 6-1 5, 18-26, 29-32, and 63 essentially comprise a pharmaceutical composition present in the form of granules or dry powder of sodium 4-phenylbutyrate or dissolved as a concentrated aqueous solution comprising sodium 4-phenylbutyrate, at least one aromatic flavoring agent, and at least one synthetic sweetening agent comprising a mixture of aspartame and potassium acesulfame being selected so as to mask substantially the bitter taste and pungent odor of sodium 4-phenylbutyrate which may be administered to treat a patient suffering from urea cycle deficiency or sickle cell anemia using a specified dose. Rubenstein and D'Silva were relied upon as described above. The Office's position is that it would have been obvious to a person of ordinary skill in the art at the time of The invention to employ aromatic flavoring agents, and specific synthetic sweetening agents aspartame and potassium acesulfame in the compositions comprising sodium 4-phenylbutyrate because 1) Rubenstein teaches that sodium 4-phenylbutyrate has a bad taste, and also teaches that the compositions comprising sodium 4-phenylbutyrate can contain flavoring agents, and artificial sweetening agents, and 2) D'Silva teaches that aspartame, acesulfame potassium, saccharin, sucralose in an amount from about 0.01 % w/v to about 5.0 % wlv of a composition, and fruit flavors such as cherry, grape, orange, strawberry or lemon in an amount from about 0.05 % to about 2.0 % by weight of the composition are employed in pharmaceutical compositions to mask the disagreeable taste of the pharmaceutically active agent.[15]

The cited references, when considered alone or in combination, fail to provide one skilled in the art with a reason to formulate a dry powder, granules, solution or concentrate as claimed, let alone with any reasonable expectation of success. The Rubenstein reference regarding sodium 4-phenylbutyrate does not suggest dosage forms as claimed, but rather only describe tablets, a dosage form which cannot be taken by children. These references also fail to disclose or

[15] Examiner's comments on page 7 in the Office Action.

suggest that the odor of the drug can be masked by the mixture of sweeteners and a flavorant as claimed. The cited references would not have led one skilled in the art to select the specific combinations of flavoring agent, and at least one synthetic sweetening agent comprising a mixture of aspartame and potassium acesulfame in the amounts to mask the pungent rodent-like odor of sodium 4-phenylbutyrate. Furthermore, the invention comprises the selection of the two sweeteners and the flavorant to avoid not only the pungent rodent-like odor but also the disagreeable taste of the sodium associated with high doses of sodium 4-phenylbutyrate. Moreover, inherency cannot be established by probabilities or possibilities and there is no evidence of record that the masking of odor by the claimed composition would have necessarily and inevitably resulted from the selection of flavoring agents and a mixture of aspartame and potassium acesulfame in a composition comprising sodium 4- phenylbutyrate. Nor is such masking of odor recognized in the art, particularly given that none of the cited references address the odor problem. In light of the above, applicant respectfully submits that claims 1-3, 6-1 5, 18-26, 29-32, and 63 are not rendered obvious by the combination over Rubenstein, in view of D'Silva.

The Examiner asserts that it would have been obvious to a person of ordinary skill in the art at the time of invention to determine or optimize parameters such as amounts of flavoring agents, sweetening agents, and binding agent employed in the composition of Rubenstein and that a person of ordinary skill in the art would have been motivated to determine such parameters using merely routine skill in the art.[16] MPEP 2144.05 makes it clear that the cited reference must recognize the parameter at issue to be a result effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of the variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Thus, only the optimization of "result-effective variables," as recognized in the prior art, might be characterized as routine. MPEP 2144.05 II B. None of the references relied on by the Examiner disclose nor suggest that the masking of the pungent

[16] Examiner's comments on pages 7- 8 in the Office Action.

rodent-like odor of sodium 4-phenylbutyrate is a result effective variable and thus it was not obvious to determine or optimize parameters such as amounts of flavoring agents, sweetening agents, and binding agent to affect the pungent rodent-like odor of sodium 4-phenylbutyrate.

Although applicant submits that a prima facie case of obviousness has not been established, applicant notes that it was also an unexpected result that the claimed compositions would be effective in masking the pungent odor of sodium 4-phenylbutyrate. As stated above, sodium 4-phenylbutyrate has an extremely salty taste which would be unacceptable to a chronically ill child. Furthermore, the daily intake of sodium 4-phenylbutyrate needed to treat a child afflicted with a urea cycle deficiency or sickle-cell anemia diseases is very high – 450-600 mg per kg of body weight.[17] Thus a 5 year old child weighing 18 kg would have to take 8.1 g to 10.8 g daily in four divided doses. The content of sodium in sodium 4-phenylbutyrate is high – 123.5 mg of sodium per 1 gram of sodium 4-phenylbutyrate based on the atomic weight of sodium being 23 grams and that of sodium 4-phenylbutyrate being 186.2 grams. Therefore, a five year old child weighing 18 kg would have to take 1.00-1.33 grams of sodium per day just in consumption of sodium 4-phenylbutyrate. This is the equivalent of taking 2.50-3.33g of salt per day when including typical dietary sodium. The UK Guidelines for salt intake in children indicate that the recommended maximum daily salt intake for a 5 year old is 3 g (i.e., 1.2 g sodium). Thus, for a 5 year old child, the maximum dose of sodium 4-phenylbutyrate delivers 1.33 g of sodium which exceeds the recommended maximum daily intake, and it is therefore advantageous that the sweeteners which applicants found to mask the odor of sodium 4-phenylbutyrate also do not further increase or exacerbate the sodium intake of the child. Aspartame is one such sweetener. However, even at the maximum acceptable daily intake, that sweetener is insufficient to mask the salty taste of the sodium 4-phenylbutyrate. The specific formulation identified by the applicant was not arrived at by simple routine trial and error; it was the result of a substantial investment in time, effort, resources, and ingenuity to discover the

[17] Specification as filed, page 5, lines 29-35.

appropriate formulation to mask the extreme saltiness of sodium 4-phenylbutyrate in addition to masking the pungent rodent-like odor and its overall bitter, nasty or disagreeable taste.

CONCLUSION

Applicant submits that the present application is in condition for allowance and requests early allowance of the pending claims. The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

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